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Appellant: Monty Krieger

Serial No.: 09/148,012 Art Unit: 1647

Filed: September 4, 1998 Examiner: Robert S. Landsman

For: *SR-BI ANTAGONIST AND USE THEREOF AS CONTRACEPTIVES AND IN THE TREATMENT OF STEROIDAL OVERPRODUCTION*

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-10, 12, 15, 16, and 19-22 in the Office Action mailed February 6, 2003, in the above-identified patent application. A Notice of Appeal was mailed on June 6, 2003. A check in the amount of $320.00 for the filing of this Appeal Brief is also enclosed. Also enclosed is a Petition for an extension of time for one month, up to and including September 6, 2003. The Examiner is hereby authorized to charge $110, the fee for an extension of time for one-month, to Deposit Account No. 50-1868. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

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(1) REAL PARTY IN INTEREST

The real party in interest of this application is Massachusetts Institute of Technology, the assignee.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-10, 12, 15, 16, and 19-22 are pending and on appeal. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

An amendment after final rejection was mailed on May 6, 2003. In the Advisory Action mailed June 5, 2003, the Examiner indicated that this amendment would be entered.

(5) SUMMARY OF THE INVENTION

The claims are directed to methods for altering fertility or treating a reproductive disorder in a female mammal in need of treatment thereof comprising administering a compound altering lipoprotein, LDL, HDL or cholesterol levels in the mammal in an amount effective to enhance or restore fertility or treat a reproductive disorder in the mammal (see page 7, lines 19-21; page 8, lines 5-13; lines 19-2, bridging pages 10 and 11; and lines 15-20, bridging pages 12 and 13). The compound may be selected to alter expression of SR-BI (decreased or increased) in a tissue (see page 10, lines 19-27). The compound may alter (increases or decreases) the binding of SR-

BI to high density lipoprotein including cholesteryl ester or other lipoproteins (page 12, lines 16-18; Example 2). The disorder may be treated by decreasing the production of steroids, differentially altering the activity of, or expression of, SR-BI in different tissues, increasing SR-BI expression in reproductive tissues (while decreasing, or not increasing, SR-BI expression in the liver) (page 12, lines 25-26; page 13, lines 14-15; page 13, lines 23-25; and lines 19-2, bridging pages 10-11). The compound may be an antibody to SR-BI (page 12, lines 24-28), or a drug that decreases production of steroids *via* selective binding to SR-BI (page 11, lines 10-17). The compound may decrease cholesterol levels to decrease steroid levels (page 12, lines 26-28).

(6) ISSUES ON APPEAL

The issues presented on appeal are:

(1) whether claims 1-10, 12, 15, 16, and 20-22 are enabled as required by 35 U.S.C. § 112, first paragraph;

(2) whether claims 1-10, 12, 15, 16, and 20-22 comply with the written description as required by 35 U.S.C. § 112, first paragraph; and

(3) whether claims 1-10, 12, 15, 16, and 20-22 are clear and definite as required by 35 U.S.C. § 112, second paragraph.

(7) GROUPING OF CLAIMS

The claims do not stand or fall together. The claims can be grouped as follows: (1) claim 1, directed to altering fertility or reproductive disorder *via* the administration of a lipoprotein, LDL, HDL, or cholesterol altering compound; (2) claims 2-7, 15, 16, 19 and 20, directed to altering fertility or reproductive disorder *via* affecting SR-BI expression or activity;

(3) claims 8-10 and 12, directed to defining the function or disorder to be altered; and (4) claims 21 and 22, directed to specific mechanisms of decreasing cholesterol levels. Reasons for this grouping and arguments for the separate patentability of groups 2, 3 and 4 are provided below.

(8) ARGUMENTS

(a) The Claimed Invention

Appellant is the first to recognize that lipoprotein and/or cholesterol levels affects a female's ability to reproduce. Appellant is the first to recognize that SR-BI, by virtue of its role as the only known transporter of cholesterol, which is critical to steroid production, plays a major role in female reproduction. Appellant demonstrated the criticality of SR-BI, and its role on lipoprotein and cholesterol levels, using SR-BI knockout mice. The homozygous knockout females are unable to carry a fetus to term. Heterozygotes are able to do so. These studies are described in the patent application as filed. Appellant has subsequently shown that treatment of the mice with a known cholesterol lowering drug such as probucal, which normalizes the cholesterol values and the lipoprotein levels, to a degree, restores fertility to these animals.

The examiner has acknowledged the novelty and non-obviousness of appellant's discovery. The issue is whether appellant is entitled to such broad claims under 35 U.S.C. 112.

The data presented in the specification clearly demonstrate that multiple compounds have been identified and can be used to restore fertility. These compounds are representative of widely disparate species, ranging from nucleic acid molecules encoding SR-BI to organic compounds for lowering cholesterol.

In example 5, appellant demonstrated that transient increases in SR-BI expression following administration of an adenoviral vector encoding SR-BI results in a decrease in cholesterol levels. In example 6, the appellant demonstrated that SR-BI knockout animals exhibit the opposite phenotype; increased cholesterol levels (see Table 3). Data in example 7 further shows that these animals are also infertile. Antibody blocking studies have also showed similar results using antibodies to block cholesterol transport, resulting in lowered cholesterol levels, as described in Example 8, page 55.

The reagents and methods provided in the present specification were used to subsequently show the restoration of fertility in an SR-BI knockout mouse (or their transplanted oocytes) in the absence of ovarian and/or extraovarian SR-BI expression by manipulations that modify the structure, composition and/or abundance of their abnormal plasma lipoproteins. These manipulations centered around the administration of probucal, a cholesterol lowering drug (see the response mailed on February 15, 2002; copy of Meittinen, *et al.*, *J. Clin. Invest.* 108:1717-1722 (2001)).

The application therefore teaches one skilled in the art that SR-BI is essential for normal female fertility; that decreasing levels of SR-BI activity decreases cholesterol levels and alters lipoprotein levels; and that restoring SR-BI activity normalized cholesterol levels and lipoprotein profiles, with a concurrent increase in steroidogenesis and female fertility. The application further teaches that one can use any number of compounds to alter SR-BI levels: viral vectors to increase SR-BI expression; antibodies to block SR-BI activity and concurrent transport of cholesterol; and organic molecules identified by routine screening assays using SR-BI binding

and uptake studies. These compounds alter SR-BI activity either by increasing the amount of transport or by decreasing transport (for example, using viral vectors or antibodies). These clearly and unequivocally affect female fertility as claimed.

(b) Rejection Under 35 U.S.C. § 112, written description

i. The Legal Standard for Written Description

Both the written description and enablement requirements are defined by 35 U.S.C. § 112, first paragraph, which states that the patent specification must contain "a written description of the invention, and of the manner and process of making and using it...[such] as to enable any person of ordinary skill in the art to which it pertains ... to make and use the same ... " The purpose of the written description requirement is to prevent a patentee from later asserting that he invented something which he did not. Thus the patentee must "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." *Vas- Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 U.S.P.Q.2d 1111, 1115 (Fed. Cit 1991).

For many years the leading case for the written description requirement in the biotechnology and pharmaceutical arts was *Eli Lilly v. Univ. of Calif. Board of Regents*, in *Regents of University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), *cert denied*, 523 U.S. 1089 (1998). The Federal Circuit evaluated whether claims to recombinant production of human insulin in U.S. Patent No. 4,652,525 met the written description requirement. The court determined that the specification failed to comply with the written description requirement for only disclosing a single species of DNA encoding non-human insulin.

The Federal Circuit has since held that that the written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure. *Enzo Biochem, Inc., v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir.2002). This standard has been reviewed and clarified further in the recent decision of *Amgen Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.* 314 F.3d 1313, 65 USPQ 2d (Fed. Cir. 2003).

ii. The Specification Complies with the Written Description Requirement

The claimed invention is based on the clear cut description of the nexus between fertility and cholesterol levels. *The specification is replete with support for this novel connection* (see, for example, page 7, lines 21-22; page 13, lines 14-15; page 49, lines 16-20; page 49, lines 21-24 and Example 7). Because of this established connection, the appellant is claiming **all** compounds that alter lipoprotein, LDL, HDL, or cholesterol levels for the purpose of altering fertility or treating a reproductive disorder in a female mammal. The examples in the specification clearly show that, for example, **antibodies** raised against a portion of the extracellular domain of the protein inhibit the selective uptake of HDL and delivery of HDL cholesterol to the steroidogenic pathway in cultured adrenal cells (Example 8, and in particular, Table 4, wherein anti-SR-BI inhibited the production of tritiated steroid derived from tritiated HDL). Adenoviral vectors encoding SR-BI (Example 5) are an additional example of a compound that has been shown to alter cholesterol levels (as will be discussed below in more detail as it relates to enablement). In **each** of Examples 3, 5 and 8, the appellant has **reduced to practice a distinct compound** for altering cholesterol levels.

In Example 6, the SR-BI gene was inactivated in embryonic stem cell by standard recombination methods (strategy shown in Example 3). Blastocysts were injected with the embryonic stem cells, producing 24 male chimeric mice. F1 offspring (from crosses between the chimeric mice and wild type females) were either homozygous or heterozygous at the SR-BI locus. ***F1 intercrosses generated F2 progeny, wherein the males were fertile and the homozygous females (-/- at the SR-BI locus) were unable to produce offspring (Example 7 further discusses the reproductive studies on these mice to make a determination regarding fertility)***. Example 6 then discusses the resultant elevated levels of plasma cholesterol in which the cholesterol and apolipoprotein profiles of the *heterozygous* mutants were similar to those of wild type controls, except that there was an increase in the amount of cholesterol in the HDL fractions. In the *F2 homozygous* mutant animals (-/- at the SR-BI locus), the cholesterol was found in a large, somewhat heterogeneous peak in the HDL range (*via* FPLC cholesterol analysis). In view of the foregoing results (as discussed in detail in Example 6), *one of ordinary skill in the art will readily recognize, not only the direct correlation that exists between cholesterol/HDL and the existence of SR-BI, but also the many compounds that already exist for regulating cholesterol levels. These compounds, well known for altering cholesterol levels, can be used to regulate fertility via the modulation of SR-BI expression or activity.*

The legal standard for written description does NOT require that the appellant reduce to practice all of the claimed species that may fall within the claimed genus. In this regard, the Board's attention is not only drawn to the three widely disparate types of compounds discussed in the foregoing paragraph, but additionally, and respectfully, drawn to the section in the

specification entitled: "I. Inhibitors of SR-BI transport of cholesterol", and the section entitled: "II. Methods of Regulation of SR-BI cholesterol transport to alter steroidogenesis". The description clearly conveys that, in addition to the classes of compounds actually used to show reduction to practice, a number of other molecules were known and could be screened for utility in the claimed method.

The test under 35 U.S.C. 112 was clearly articulated by the Court in *Amgen Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.* 314 F.3d 1313, 65 USPQ 2d (Fed. Cir. 2003) as being different in the case where, as here, the reagents that could be used in a claimed method were known, and where one was claiming a novel class of compounds. The Court weighed heavily the fact that one was not claiming the class of compounds *per se*, but the use of the compounds. A different degree of description is required where compounds are known and one only needs to provide the criteria for their selection and use - a degree clearly met by appellant.

(c) Rejection Under 35 U.S.C. § 112, enablement

i. The Legal Standard for Enablement

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation (*See, e.g., Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v.*

Telectronics, Inc., 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). There is no requirement for examples.

ii. <u>The Specification Complies with the Enablement Requirement</u>

The appellant is somewhat confused by the language recited in the Advisory Action, stating "...Appellants are only enabled for the compounds and methods for which they have claimed" (see page 2 of the Advisory Action mailed on June 5, 2003). We agree.

As discussed above, the claims are based on the discovery of *the nexus between fertility and cholesterol levels. The specification is replete with support for this novel connection* (see, for example, page 7, lines 21-22; page 13, lines 14-15; page 49, lines 16-20; page 49, lines 21-24 and Example 7). Because of this established connection, the appellant is claiming **all** compounds that alter lipoprotein, LDL, HDL, or cholesterol levels for the purpose of altering fertility or treating a reproductive disorder in a female mammal. One can readily identify patients to be treated: those females that are infertile and who have elevated cholesterol and/or abnormal lipoprotein levels. Not all females who are infertile will be characterized by elevated cholesterol and/or abnormal lipoprotein levels, and therefore will not be patients in need of treatment as claimed. The first end point in the treatment will be normalization of cholesterol and/or lipoprotein levels; the second, and corollary of the first is restoration of fertility. Both are readily ascertained.

It should be noted that the class of patients is relatively small and does not overlap with the normal class of patients treated with drugs altering cholesterol and/or lipoprotein levels. Most of these individuals are older - in the case of women, cholesterol does not typically increase until after menopause.

The examples have been discussed above. The paper showing restoration of fertility by administration of a cholesterol lowering drug, probucal, also discussed above, provides further

support for the claimed method. The mere fact that this data was obtained after the filing date of the application makes the data no less relevant for demonstrating enablement. The role of SR-BI in fertility is clearly established by the examples in the specification. The role of SR-BI in cholesteryl transport was known (see, page 10, lines 19-21). The alterations in lipoprotein and cholesterol levels in the SR-BI deficient animals is established (see Table 1). The Example provided by the appellant in the post-filing publication (see journal article enclosed with the response mailed on February 15, 2002; Meittinen, *et al.*, *J. Clin. Invest.* 108:1717-1722 (2001)), uses Probucal, a well-known cholesterol lowering drug, which confirms that one can normalize the lipoprotein and cholesterol levels in these animals and restore fertility. Other cholesterol lowering drugs are available. One skill in the art would have no trouble obtaining drugs that alter lipid levels using standard pharmaceutical texts. These are administered at a recommended dosage and the effect on the lipid levels measured. None of the foregoing would require undue experimentation.

The appellant respectfully asserts that one of skill in the art would understand from the specification which compounds to use, and how to derive appropriate doses with minimal routine experimentation to practice the claimed method and alter fertility or treat a reproductive disorder.

(d) Rejection Under 35 U.S.C. § 112, clarity

i. The Legal Standard under 35 U.S.C. § 112, second paragraph

In reviewing a claim for compliance with 35 U.S.C. § 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35

U.S.C. § 112, second paragraph. *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 137, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). The examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. § 112, second paragraph is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available. "Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire." M.P.E.P. § 2173.02.

ii. Claims 1-10, 12, 15, 16 and 20-22 are definite as required by 35 U.S.C. § 112, second paragraph.

The issue appears to be the use of the phrase "enhanced or restored". One of ordinary skill in the art will readily be able to ascertain whether fertility is enhanced or restored. As shown in Example 6, no offspring from female homozygous mutants have been obtained following multiple attempts to do so, indicating a substantial, and possibly complete, decrease in fertility in these females. In the F2 progeny (described above), the observed ratios of wild-type heterozygous : mutant heterozygous : mutant homozygous were 1.0:1.7:0.5; values significantly different from the expected Mendelian ratio of 1:2:1. This indicated that there may be partially penetrant effects of the mutation either on neonatal survival or on embryonic development, which would be consistent with the distribution of SR-BI on the maternal surfaces of cells in the placental and yolk sac during embryonic development. Because of the potential for ***partially*** penetrant effects on neonatal survival or on embryonic development, it is appropriate to use the

term "enhanced" to describe a level of fertility in a population that has been treated, not just "restored".

(e) The Examiner has failed to individually examine the dependent claims

It is well established that each claim must be separately examined for patentability. It is not enough, as here, to look at a single independent claim and reject all claims. No rationale has been presented as to why the subject matter of claims 2-7, 15, 16, 19, and 20, directed to altering fertility or reproductive disorder *via* affecting SR-BI expression or activity, are not enabled. No rationale has been presented as to why the subject matter claims 21 and 22 are not enabled. The issues are different with respect to enabling a method for altering fertility *via* SR-BI expression or activity; and altering fertility *via* generally decreasing cholesterol levels. Furthermore, no rationale has been presented as to why the subject matter of claims 8-10 and 12, drawn to a method of decreasing fertility by decreasing cholesterol available for steroidogeneis is not enabled.

No rationale has been presented as to why claims 2-7, 15, 16, 19, and 20 , directed to altering fertility or reproductive disorder *via* affecting SR-BI expression or activity; claims 8-10 and 12, directed to defining the function or disorder to be altered; and claims 21 and 22, directed to specific mechanisms of decreasing cholesterol levels, lack proper written description support. The issues relating to a proper written description are different for each of the foregoing groups.

The same is true with respect to the rejection for lack of clarity. No basis has been provided for rejection of the dependent claims.

(9) SUMMARY AND CONCLUSION

It has been estimated that for 10-20% of women with infertility problems, the underlying causes are unknown. Because HDL is the only lipoprotein present in substantial amounts in the follicular fluid surrounding the developing oocyte in humans, based on the data in the examples and paper provided by appellant, it is expected that changes in HDL and/or SR-BI in humans may disturb oocyte maturation or function, and thus contribute to infertility. The present application, and its analysis of SR-BI knockout mice, ties together fertility and cholesterol level. The direct correlation that exists between cholesterol/HDL and the existence of SR-BI, lies at the core of the claimed method. Many compounds that already exist for regulating cholesterol levels can be used to alter fertility *via*, for example, the modulation of SR-BI expression or activity. It would not require undue experimentation to identify these compounds, the patients to be treated, or what constitutes an effective amount. Moreover, one skilled in the art would have no difficulty in identifying the scope of the claimed method in view of the specification, the examples, and the knowledge available to those skilled in the art.

For the foregoing reasons, Appellant submits that the claims 1-10, 12, 15, 16, and 19-22 are patentable.

Respectfully submitted,

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Date: September 8, 2003

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I hereby certify that the Appeal Brief, along with any papers referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to Mail Stop Appeal Brief-Patents, Commissioner for Patents, P. O. Box 1450, Alexandra, VA 22313-1450.

Rivka D. Monheit

Date: September 8, 2003

Appendix: Claims On Appeal

1. (previously twice amended) A method for altering fertility or treating a reproductive disorder in a female mammal in need of treatment thereof comprising

administering a compound altering lipoprotein, LDL, HDL or cholesterol levels in the mammal in an amount effective to enhance or restore fertility or treat a reproductive disorder in the mammal.

2. (previously amended) The method of claim 1 wherein the compound alters SR-BI expression in a tissue.

3. (original) The method of claim 1 wherein the compound alters binding of SR-BI to high density lipoprotein including cholesteryl ester or other lipoproteins.

4. (previously amended) The method of claim 2 wherein the compound decreases SR-BI expression in the tissue of the mammal.

5. (previously amended) The method of claim 2 wherein the compound increases SR-BI expression in the tissue of the mammal.

6. (previously amended) The method of claim 3 wherein the compound decreases SR-BI binding to lipoprotein or transfer of cholesteryl ester in the tissue of the mammal.

7. (previously amended) The method of claim 3 wherein the compound increases SR-BI binding to lipoprotein or transfer of cholesteryl ester in the tissue of the mammal.

8. (original) The method of claim 1 wherein the mammal is a female and the compound is administered in an amount effective to prevent normal reproductive function.

9. (previously amended) The method of claim 1 wherein the mammal has a disorder characterized by an overproduction of steroids.

10. (previously amended) The method of claim 1 wherein the mammal has a disorder characterized by an underproduction of steroids.

12. (original) The method of claim 1 wherein the mammal has a disorder which can be treated by decreasing production of steroids.

15. (original) The method of claim 1 wherein the compound differentially alters the activity of, or expression of, SR-BI in different tissues.

16. (original) The method of claim 11 wherein the compound increases SR-BI expression in reproductive tissues and decreases or does not increase SR-BI expression in liver.

19. (withdrawn) The method of claim 1 wherein the compound is an antibody to SR-BI.

20. (previously added) The method of claim 1 wherein the compound is a drug that decreases production of steroids via selective binding to SR-BI.

21. (previously added) The method of claim 20 wherein the compound decreases cholesterol levels to decrease steroid levels.

22. (previously added) The method of claim 21 wherein the compound inhibits cholesterol transport.

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